



COMBRETUM ERYTHROPHYLLUM (BURCH.) SOND. (COMBRETACEAE): A REVIEW OF ITS ETHNOMEDICINAL USES, PHYTOCHEMISTRY AND PHARMACOLOGY

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Abstract

Combretum erythrophyllum (family: Combretaceae) is a tree that is highly valued in southern Africa. Numerous ethnomedicinal and pharmacological properties have been attributed to it. Pharmacological studies conducted by different investigators have revealed that *C. erythrophyllum* possesses antibacterial, antifungal, anti-inflammatory, genitor-urinary, cytotoxic and mutagenic properties. The results of some of these studies support the ethnotherapeutic use of the plant in traditional medicine. This review was done to highlight all the information available on *C. erythrophyllum*.

Key words: *Combretum erythrophyllum*, ethnomedicinal, pharmacological properties, mutagenic

Introduction

Combretum erythrophyllum (Burch.) Sond. (Family: Combretaceae) popularly known in English as “river bush tree”, in Shona as “Chitiswati” and in Ndebele as “Umdubu”, is widely used in traditional medical practice in southern Africa (Gelfand *et al.*, 1985, Sohin and Kale, 1997). The tree is native to the northeastern part of southern Africa, from Zimbabwe in the north, down to the Eastern Cape in the south (Mthethwa, 2009). It is a riverine species, occurring alongside rivers or other areas where sufficient groundwater is available. The tree is highly valued in southern Africa due to its ethnomedicinal properties.

C. erythrophyllum is a multi-stemmed, medium to large densely foliated deciduous tree that can reach 12m in height (Gelfand *et al.*, 1985). The branches grow out horizontally, sometimes lying on the ground and with a large number of upright branches sprouting up from these (Martini, 2001). The bark is a greyish-brown colour and often has irregular patches of bark which have flaked off to expose grey patches of new bark. When mature, the leaves are a dark shiny green colour as opposed to the young leaves which are yellow (Watt, J.M. and Breyer-Brandwijk, 1962), and they turn red in autumn, hence the name *erythrophyllum*. The flowers, which appear once the new leaves have appeared, are greenish-yellow and are lightly scented. They emerge in dense auxiliary spikes of about 10 mm in diameter. The 4 winged fruit, which is between 10-15 mm in length, changes colour from green to yellow-brown when it ripens (van Wyk and van Wyk, 1997). The seeds which are found in the winged fruit capsules are poisonous.

Ethnomedicinal uses

Throughout southern Africa different parts of the plant are used to treat different conditions. Root, stem and bark decoctions are used to treat leprosy (Pettit *et al.*, 1987) and are also used as a cure for coughs (Schemelzer and Gurib-Fakim, 2013); while leaf infusions are used to treat abdominal pains (Hutchings *et al.*, 1996). The Zulu people in South Africa administer small doses of *C. erythrophyllum* to their dogs as a fattening tonic (Sohin and Kale, 1997), whereas the gum is used as a food adulterant by many (Anderson and Morrison, 1990). In addition, the gum can also be dried, powdered and used on wounds. Though the seeds are poisonous and can cause continuous hiccups, some cultures use them to purge dogs of intestinal worms (Schemelzer and Gurib-Fakim, 2013).

In Zimbabwe, powdered roots of *C. erythrophyllum* are inserted vaginally as an aphrodisiac and to reduce the size of the vaginal orifice (Gelfand *et al.*, 1985). The roots and/or the leaves are also inserted into the vagina as a cure and prophylactic for venereal diseases, and as a purgative when one is constipated (Hutchings *et al.*, 1996, Van Wyk *et al.* 2000). In Zulu medicine, seed and root decoction are taken during pregnancy to facilitate delivery, while bark decoctions are taken to treat infertility (Hutchings *et al.*, 1996). These practices however, are not recommended as many women have died after vaginal insertion of powdered roots or bark, with symptoms including abdominal pain, severe vomiting and confusion (Mavi, 1996, Hutchings *et al.*, 1996). **Table 1** summarizes the use of the plant in southern Africa.

Table 1: Some of the ethnomedicinal uses of *Combretum erythrophyllum* in southern Africa.

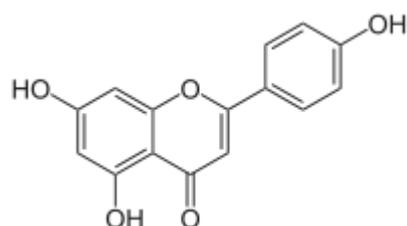
<u>Part of the plant used</u>	<u>Ethnomedicinal use</u>	<u>Reference</u>
Root	<ul style="list-style-type: none"> • Aphrodisiac • Decrease size of vaginal orifice • Treat/prevent venereal diseases • Facilitate delivery • Treat leprosy • Relieve constipation (as a purgative) • Cure coughs 	<ul style="list-style-type: none"> • Gelfand <i>et al.</i>, 1985 • Gelfand <i>et al.</i>, 1985 • Hutchings <i>et al.</i>, 1996, Van Wyk <i>et al.</i> 2000 • Hutchings <i>et al.</i>, 1996 • Pettit <i>et al.</i>, 1987 • Hutchings <i>et al.</i>, 1996, Van Wyk <i>et al.</i> 2000). • Schemelzer and Gurib-Fakim, 2013
Stem bark	<ul style="list-style-type: none"> • Treat leprosy • Treat infertility • Cure coughs 	<ul style="list-style-type: none"> • Pettit <i>et al.</i>, 1987 • Hutchings <i>et al.</i>, 1996 • Schemelzer and Gurib-Fakim, 2013
Leaves	<ul style="list-style-type: none"> • Treat/prevent venereal diseases • Treat abdominal pain 	<ul style="list-style-type: none"> • Schemelzer and Gurib-Fakim, 2013; • Hutchings <i>et al.</i>, 1996; Van Wyk <i>et al.</i> 2000 • Hutchings <i>et al.</i>, 1996
Seeds/Fruit	<ul style="list-style-type: none"> • Facilitate birth • Anthelmintic 	<ul style="list-style-type: none"> • Hutchings <i>et al.</i>, 1996 • Schemelzer and Gurib-Fakim, 2013;

Other uses

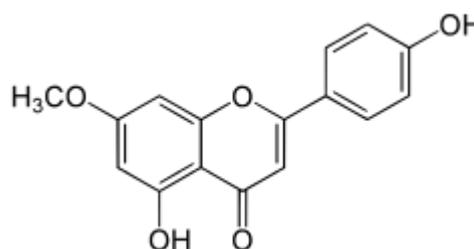
Besides the ethnopharmacological uses, *Combretum erythrophyllum* is a versatile tree with many other uses. The gum which is non-toxic and elastic is used as a varnish on furniture (Van Wyk and Van Wyk, 1997). Previously it was used in tanneries as a substitute for gum from *Astragalus spp* (Schemelzer and Gurib-Fakim, 2013). The roots which produce a dark rich dye are also used in tanneries to tan hides. Wood obtained from *C. erythrophyllum* is tough and easily worked with such that people in rural areas use it to make cattle troughs, grain mortars, household utensils and ornaments as well as for firewood (Dyer, 1996). Though fruit from *C. erythrophyllum* is poisonous, dried fruits are used as household ornaments.

Phytochemistry

Phytochemical screening of *C. erythrophyllum* leaf extracts using different solvents, mainly acetone, chloroform, methanol, dichloromethane and ethanol, revealed the presence of polyphenols, flavonoids, triterpenoids and saponins. Martini *et al.* (2004) identified seven different flavonoids present in *C. erythrophyllum* which are believed to be responsible for its antibacterial effect. Of these seven compounds, three were flavones, namely apigenin, genkwain and 5-hydroxy-7,4'-dimethoxyflavone, and four were the flavonols kaempferol, rhamnocitrin, rhamnazin and quercetin-5,3'-dimethylether. Seven triterpenoid acids and lactones were also isolated in the search for compounds responsible for the toxicity of this plant by Rogers (1998). The triterpenoids isolated from *C. erythrophyllum* seem to belong almost exclusively to two distinct groups, namely 30-carboxy-1 α -hydroxycycloartanes and 29-carboxy-1 α -hydroxyoleanes. More recently a series of stilbenes and dihydrostilbenes (combretastatins) with potent cytotoxic activity and acidic triterpenoids (e.g. erythrophyllic acid) and their glycosides with molluscicidal, antifungal and anti-inflammatory activity have been isolated from *Combretum* species (de Morais Lima *et al.*, 2012). Figure 1 summarises some of the phytochemicals present in *C. erythrophyllum*.



Apigenin



Genkwain

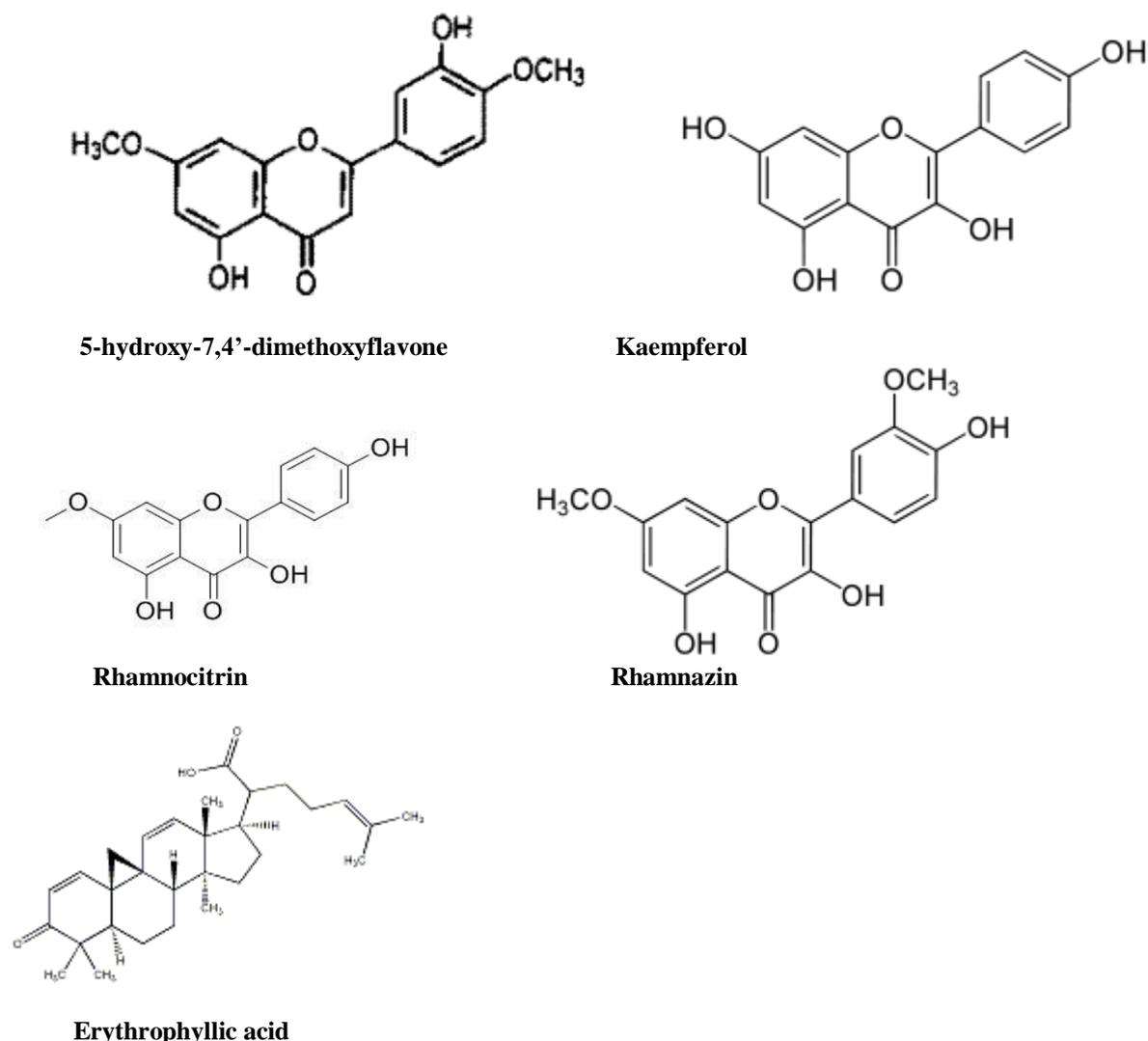


Figure 1: Some of the flavonoids present in *C. erythrophyllum*

Pharmacological activity

Antibacterial

Numerous studies have been done to investigate the antibacterial effects of *C. erythrophyllum* using different organisms. In 1998, Eloff conducted a study to determine the effects of using dried leaves of *C. erythrophyllum* extracted using different solvents (i.e. acetone, ethanol, methanol, methylenedichloride, methanol:chloroform:water and water at a 1 to 10) on *Staphylococcus aureus*. Dilution and bioautographic TLC system assay revealed that the acetone extract inhibited *S. aureus* growth the most (Eloff, 1998). In another study by Eloff (1999), microdilution assays using acetone extracts of the dried leaves on *S. aureus*, *Pseudomonas aeruginosa*, *Enterococcus faecalis* and *Escherichia coli*, revealed that *C. erythrophyllum* was active against these organisms and had a minimal inhibitory concentration (MIC) value of 1.5mg/ml, 1.5mg/ml, 1.5mg/ml and 0.8mg/ml respectively. Martini *et al.* (2004) also conducted a study to determine the effects of five antibacterial flavonoids from *C. erythrophyllum* on *Vibrio cholera*, *Enterococcus faecalis*, *Micrococcus luteus*, *Shigella sonnei* and *Escherichia coli*. In this study the flavonoids isolated inhibited the growth of the organisms at similar levels and MIC values ranged between 25 and 100 µg/ml.

The antibacterial effect has been attributed to the effects of the different phenolic substances present in *C. erythrophyllum*. According to Martini *et al.* (2004), it is assumed that the function of phenolic substances in tissues where they accumulate might be to provide chemical barriers to invading microorganisms. It has been postulated that the methylated, lipophilic flavonoids are especially suitable as protection against microorganisms because of the ease with which they penetrate bacterial cells (Williamson *et al.*, 2000).

Antifungal effect

In a study by Masoko *et al.* (2007), leaf samples of *C. erythrophyllum* were exposed to *Candida albicans*, *Cryptococcus neoformans*, *Sporothrix schenckii*, *Aspergillus fumigatus* and *Microsporium canis*. The samples were extracted using acetone, hexane, dichloromethane (DCM) or methanol. Serial microdilution assays were then used to determine the MIC values for the different plant extracts using tetrazolium violet reduction as an indicator of growth. The results obtained showed that all four extracts of *C. erythrophyllum* had antifungal effects. Acetone extracts, however, showed the best results with MIC values of ≥ 2.5 mg/mL against four of the fungal species. Rogers and Verotta, (1996)

attributed the antifungal effects of *C. erythrophyllum* to the acidic triterpenoids and their glycosides found abundantly in the leaves.

Anti-inflammatory/oxidising effects

In an *in vitro* study by Masoko *et al.* (2001), a cyclooxygenase-1 (COX-1) bioassay was used to investigate the anti-inflammatory activity of water, acetone and ethyl acetate extracts of *C. erythrophyllum*. Inhibition of COX-1 and hence of prostaglandin synthesis by the extracts was determined by detecting the conversion of radiolabelled [¹⁴C]arachidonic acid to labelled prostaglandins (Masoko *et al.*, 2001). Water, acetone and ethyl acetate extracts produced COX-1 inhibition of 21%, 67% and 92% respectively, indicating that the plant does have an effect on inflammation. In another study, Martini (2002) used a chemiluminescence assay to determine the effects of acetone leaf extracts on lymphocytes. In this study, oxidizing compounds in the extract converted luminol to an excited amonophthalate ion and this reaction was observed as a blue light when it was measured by the chemiluminometer. Observations by the author indicated that the results were linked to the different flavonoids present in the plant extract. In addition, it is well known that flavonoids inhibit inflammation by decreasing the release of inflammatory mediators and by stabilizing cell membranes (Berkoff, 1998). This could possibly account for the observed results.

Genito-urinary activity

Lindsey *et al.* (1998) conducted a study to determine the effects of ten plants used by Southern African traditional healers for the treatment of menstrual pains. *C. erythrophyllum* was amongst those screened for prostaglandin-synthesis inhibition, and the ability to reduce isolated uterine muscle contraction using cyclooxygenase and *in vitro* uterine bioassays, respectively. *C. erythrophyllum* leaves were extracted using either water or ethanol to produce 20 mg residue/ml ethanol and 2.5 mg residue/ml water. The water and ethanol extracts of the plant resulted in 26% and 90% prostaglandin synthesis inhibition respectively. The ethanolic extracts also resulted in inhibition of acetylcholine smooth muscle contractility. Although the findings of the study did not provide conclusive mechanistic evidence, the author postulated that the results could be attributed to the phytochemistry of the plant.

Cytotoxicity effects

Schwikkard *et al.* (2000) also conducted numerous *in vitro*-DNA damage cell culture assays to determine the effects of dried wood methanol extracts of *C. erythrophyllum* on yeast cells. In this study, the authors found that the extract showed reproducible inhibitory bioactivity, with IC₅₀ values of 3.6 µg/mL against RS321NYCp50 grown on galactose, 15.4 µg/mL against RS321NpRAD52 on glucose, and >100 µg/mL against RS321NpRAD52 on galactose. In addition, bioassay-guided fractionation of this extract yielded two known bioactive compounds, combretastatin A-1 and (-)-combretastatin, and two new bioactive glucosides, combretastatin A-1 2-β-D-glucoside (compound **1**) and combretastatin B-1 2-β-D-glucoside (compound **2**). Combretastatin A-1, (-)-combretastatin, and compound **1** showed reproducible and selective inhibitory activity against the DNA repair deficient strain pRAD52 (glucose), while compound **2** had no effect.

Mutagenicity

In a study by Sohni *et al.* (1994), mutagenicity studies were conducted using powdered dried root aqueous extracts of *C. erythrophyllum*. These extracts were tested using *Salmonella typhimurium* strains TA97a, TA98, TA100 and TA102. *C. erythrophyllum* (concentrations 40.0, 70.0, 80.0, 90.0, 100.0 µg/disc) was found to be mutagenic to strain TA100 and TA102. The presence of the S9 mix also enhanced the mutagenicity of *C. erythrophyllum* against strain TA100. In a separate study by Sohni and Kale (1997), sex-linked recessive lethal (SLRL) tests were done *in vitro* to evaluate its mutagenicity in *Drosophila melanogaster*. It was observed that the aqueous extract caused mutations in the meiotic stage of *Drosophila melanogaster* and had an LD₅₀ dose of 1mg/ml. The authors did not isolate the active therapeutic ingredient therefore the agent responsible for this effect is still speculative.

Table 2: Summary of the pharmacological effects of *Combretum erythrophyllum*.

Pharmacological activity	Morphological part tested	Observation	Reference
Antibacterial	Dried leaves	Active against <i>E.coli</i> , <i>E. faecalis</i> , <i>P. aeruginosa</i> , <i>S. aureus</i> , <i>V. cholera</i> , <i>M. luteus</i> , and <i>S. sonei</i>	Eloff (1998), Eloff (1999), Martini <i>et al.</i> (2004).
Antifungal	Dried leaves	Active against <i>C. albicans</i> , <i>C. neoformans</i> , <i>S. schenckii</i> , <i>A. fumigates</i> , and <i>M. canis</i>	Rogers and Verotta (1996), Masoko <i>et al.</i> (2007)
Anti-inflammatory/oxidizing	Dried leaves	COX-1 enzyme inhibition	Masoko <i>et al.</i> (2001), Martini (2002)
Genito-urinary	Dried leaves	Prostaglandin synthesis inhibition; and inhibition of acetylcholine smooth muscle contractility.	Lindsey <i>et al.</i> (1998),
Cytotoxicity	Dried roots	Inhibitory bioactivities in a yeast-based microtiter assay for DNA-damaging agents	Schwikkard <i>et al.</i> (2000)
Mutagenicity	Dried roots	Mutagenic to <i>S. typhimurium</i> strains TA100 and TA102	Sohni <i>et al.</i> (1994)

Conclusion

The present review has highlighted the ethnomedicinal, pharmacological, and phytochemical, significance of *C. erythrophyllum* in southern Africa. Further studies however, using stem bark extracts are required as currently there are no reported studies using this particular part of this plant.

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